Hematopoietic stem cell transplantation in chronic granulomatous disease

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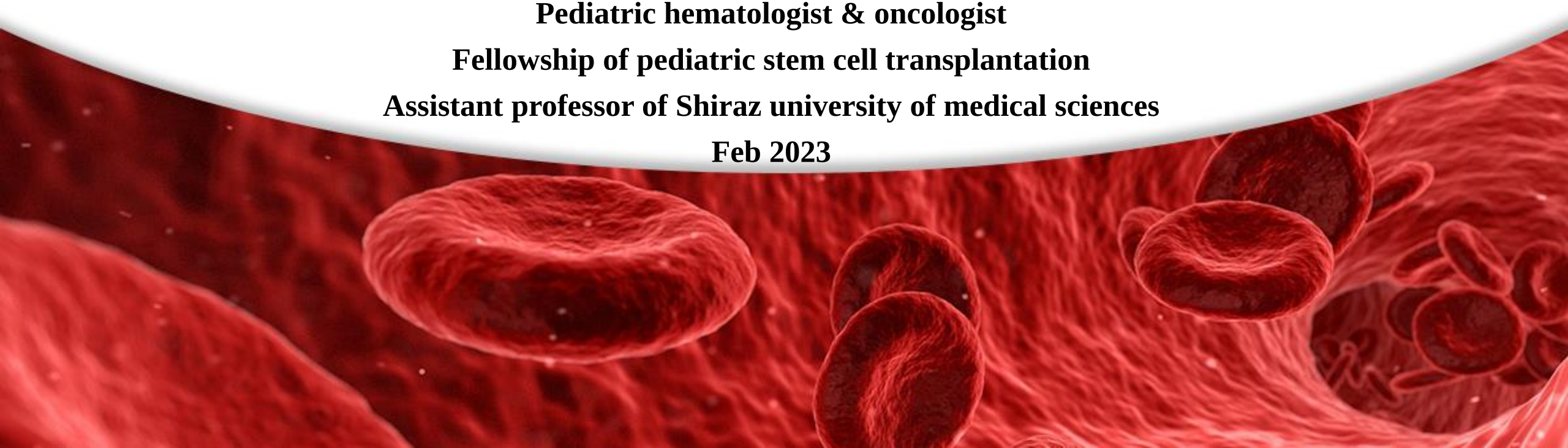
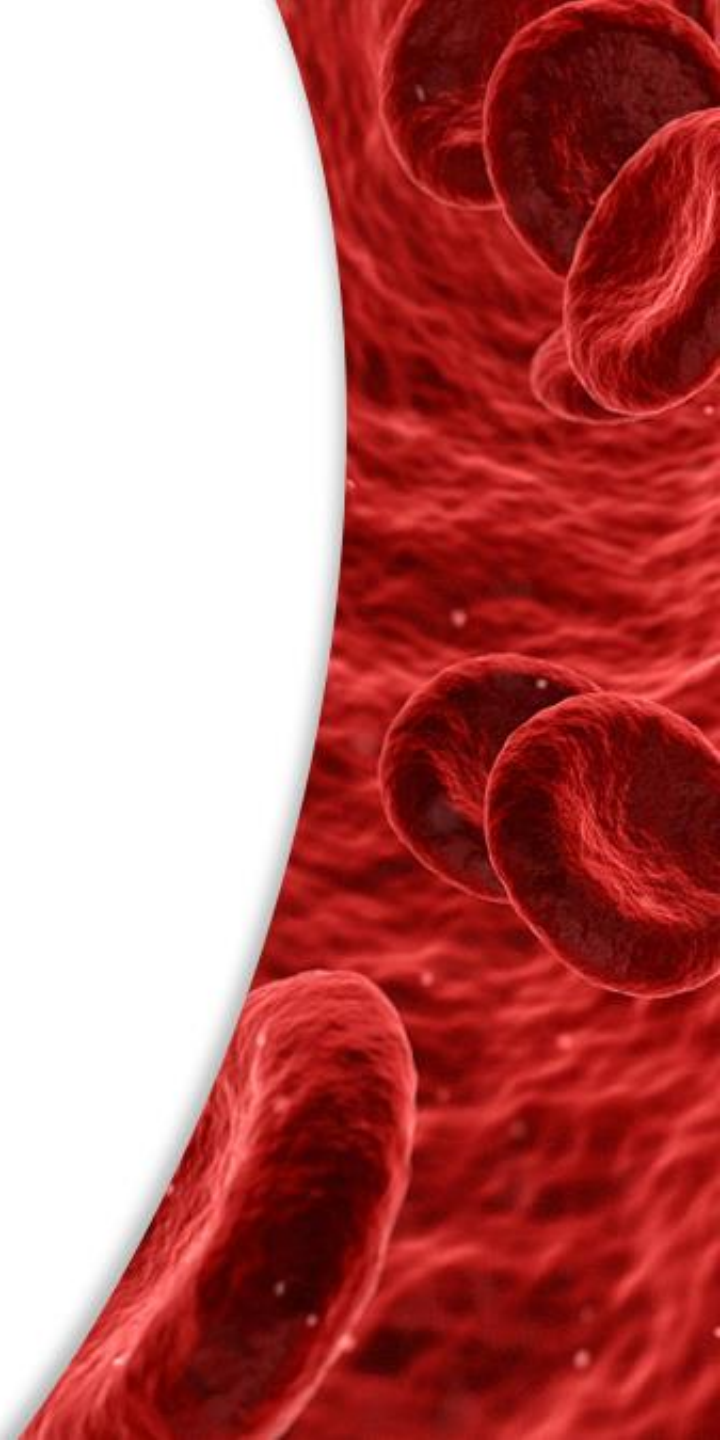


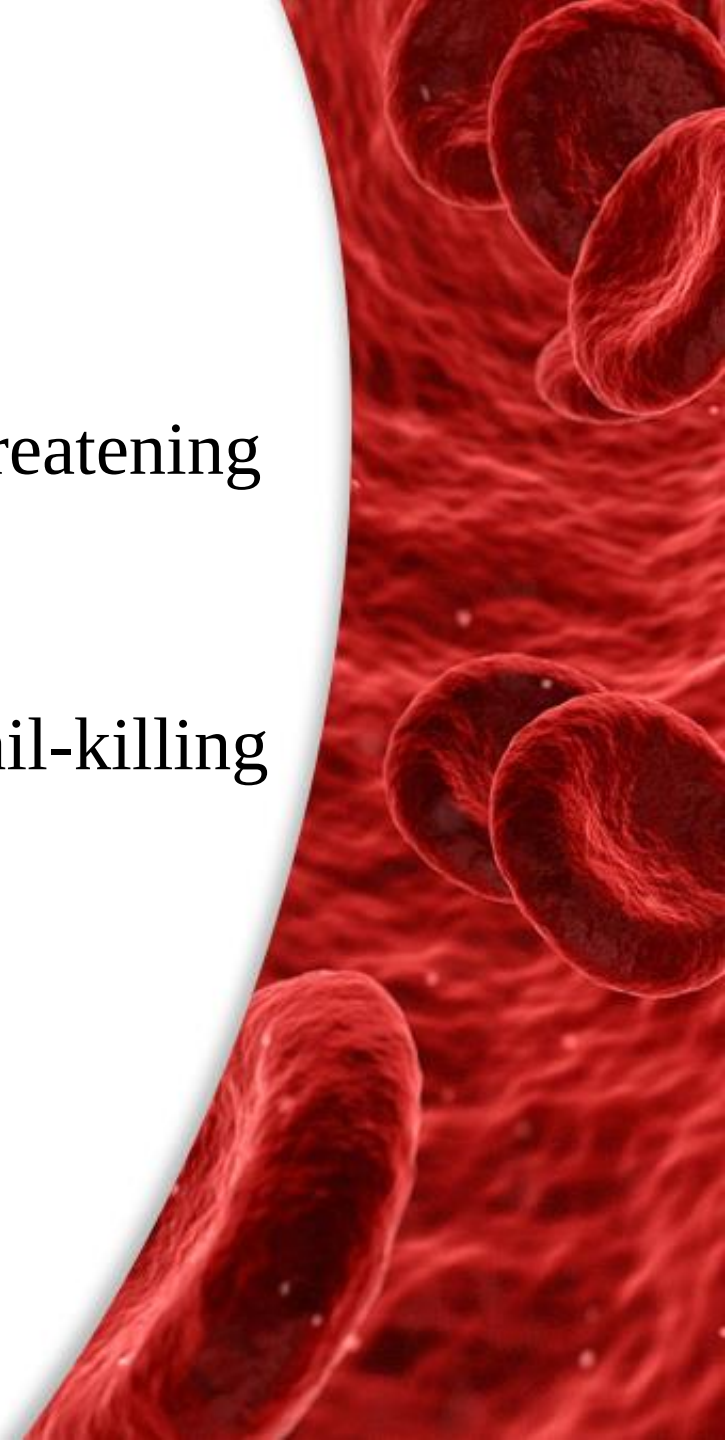
Introduction

- First described in 1954 in children who suffered from recurrent infections.
- Since then, our understanding of the epidemiology, clinical presentation and pathophysiology has significantly advanced.



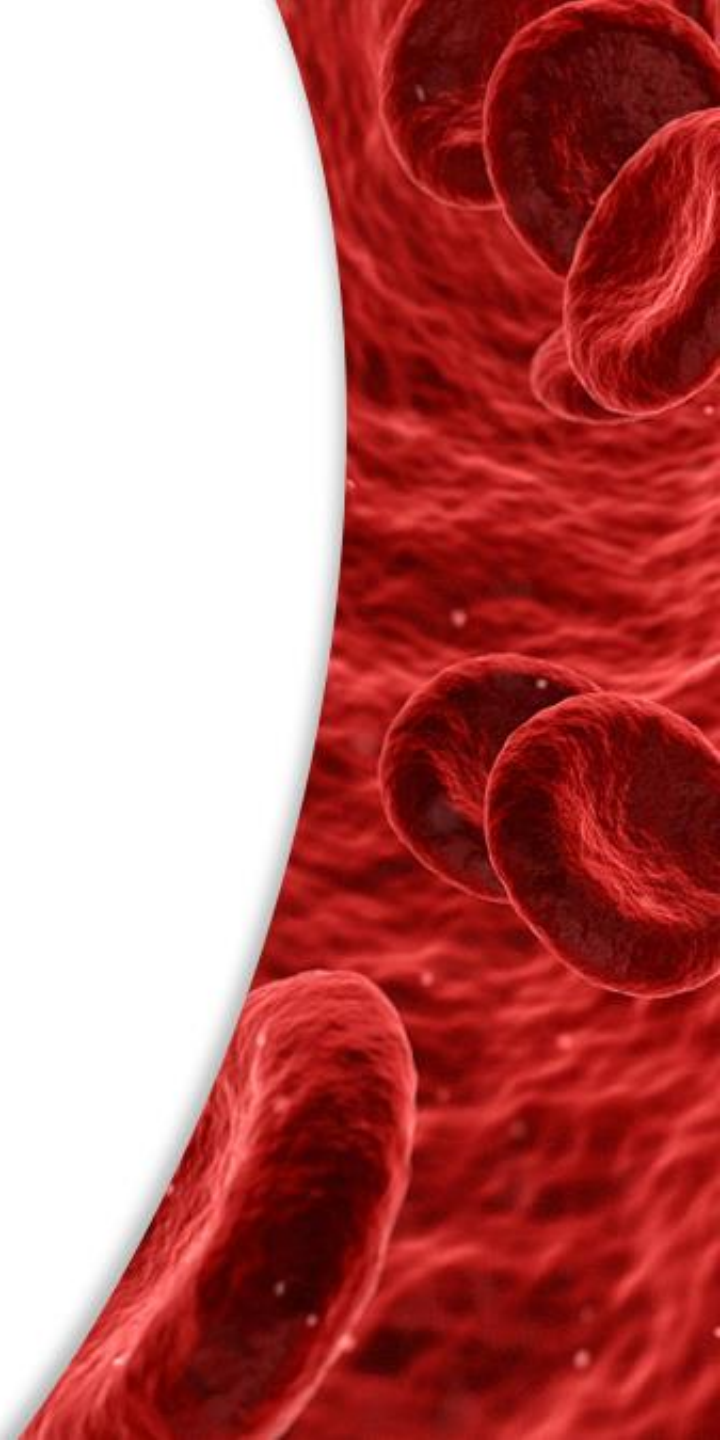
Introduction

- Congenital disorder characterized by recurrent life-threatening bacterial and fungal infections.
- Congenital defect in NADPH oxidase complex.
- Mutations in these genes lead to crippling of neutrophil-killing mechanisms that depend on NADPH oxidase activity.



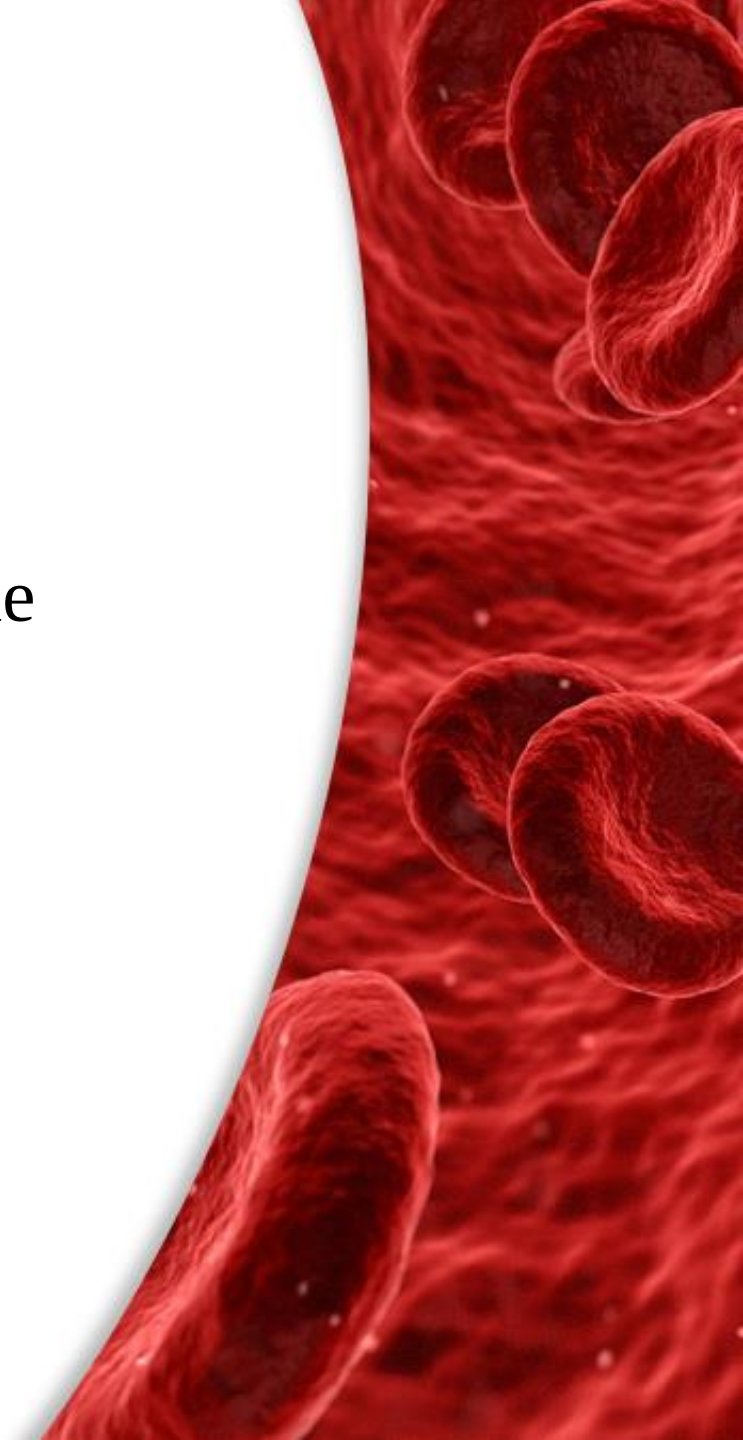
Introduction

- Patients have increased susceptibility to infections by catalase-producing organisms (such as Staphylococcus, Burkholderia, Serratia, Nocardia, and Aspergillus) with predilection for the lungs, liver, and soft tissue.
- Dysregulation of pro-inflammatory cascades and defective apoptosis predispose patients to non-infectious granulomata, typically in the lungs and gastrointestinal and genitourinary tracts.



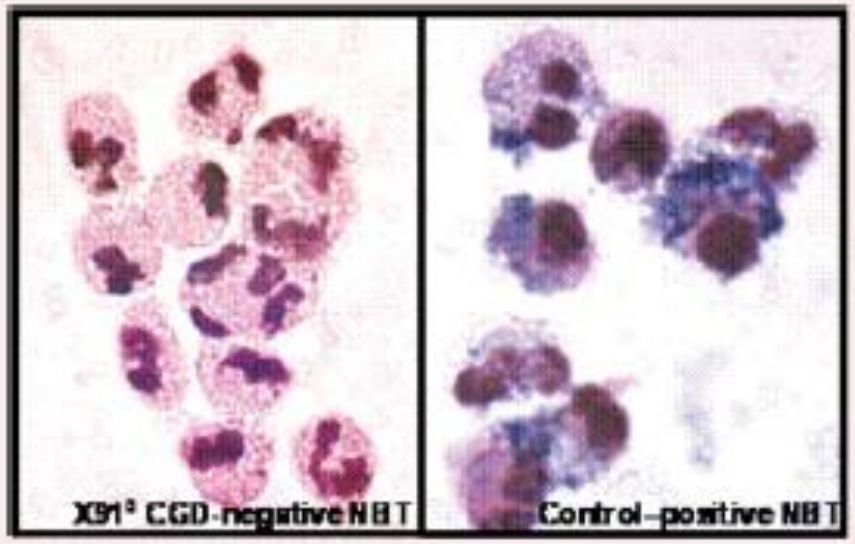
Introduction

- The second-most common PID in Middle-Eastern countries such as Iran, and accounts for 20% of these patients, with the AR form of CGD (AR-CGD) being the most common.
- Although the exact incidence of CGD in Iran is unknown, in the USA and Western Europe it is about 1 case per 200,000–250,000 live births.
- CGD is generally diagnosed in infancy or childhood.
- The mean age of detection in Iran is 5.5 years.



Diagnosis – Qualitive test

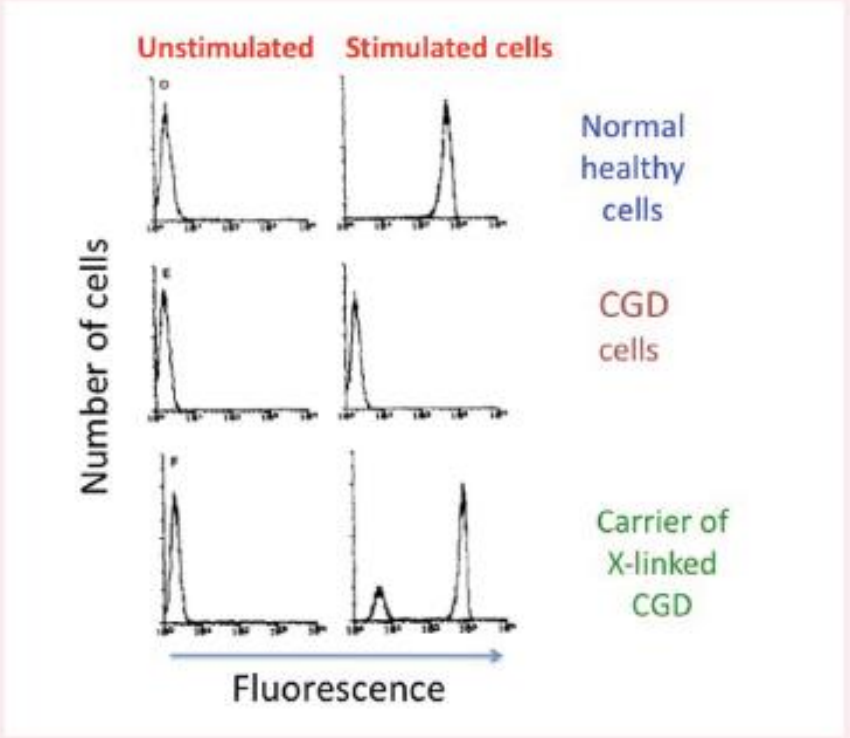
Nitroblue tetrazolium test (NBT): Neutrophils are stimulated with phorbol myristate acetate and incubated with the yellow dye nitroblue tetrazolium. Normal phagocytes reduce this to the dark blue pigment, formazan. Cells are analysed by microscopy, which requires an experienced observer. Carrier mothers of the X-linked type of CGD are identified by a mixed population of NBT+ve and NBT-ve cells.



Diagnosis of CGD by the NBT test

Diagnosis - Quantitative

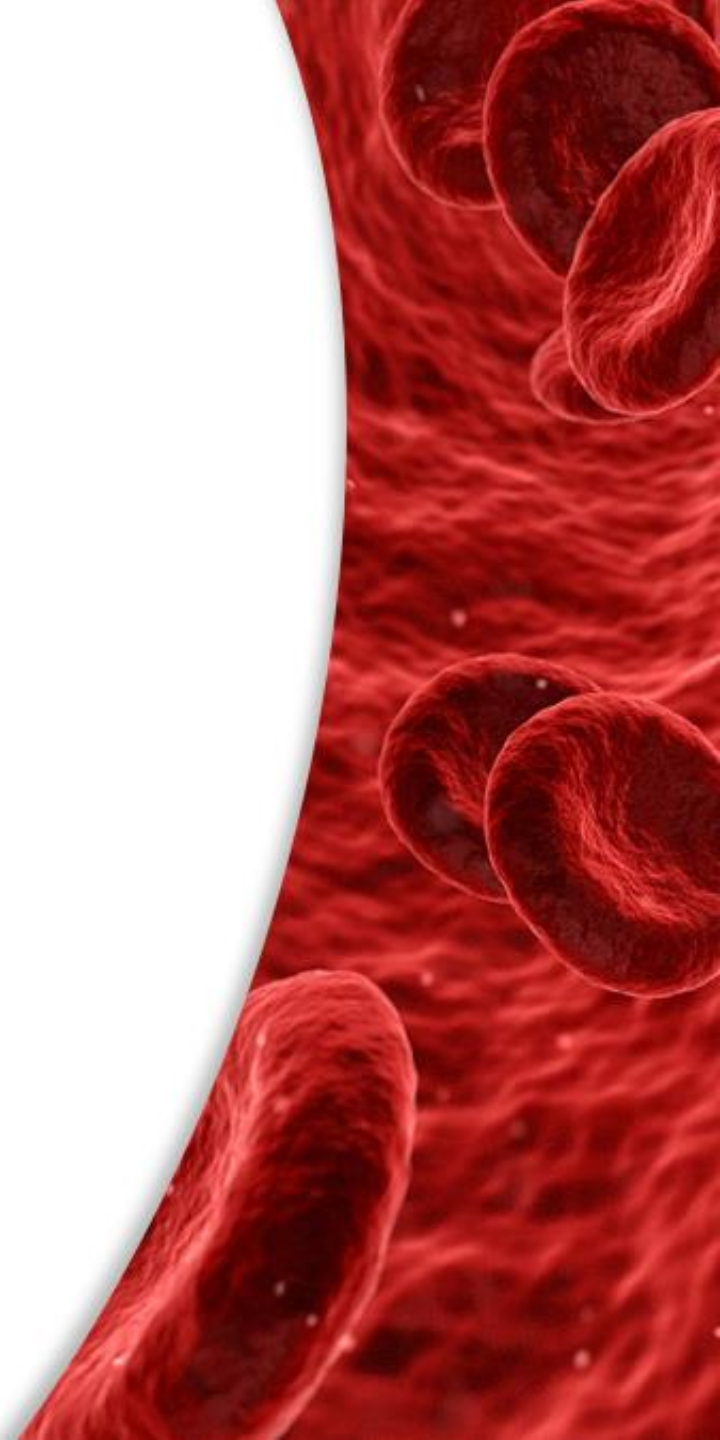
Flow cytometric reduction of dihydrorhodamine:
The principles are the same as the NBT test, but using a different dye. X-linked carrier status can also be detected.



Diagnosis of CGD by flow cytometry

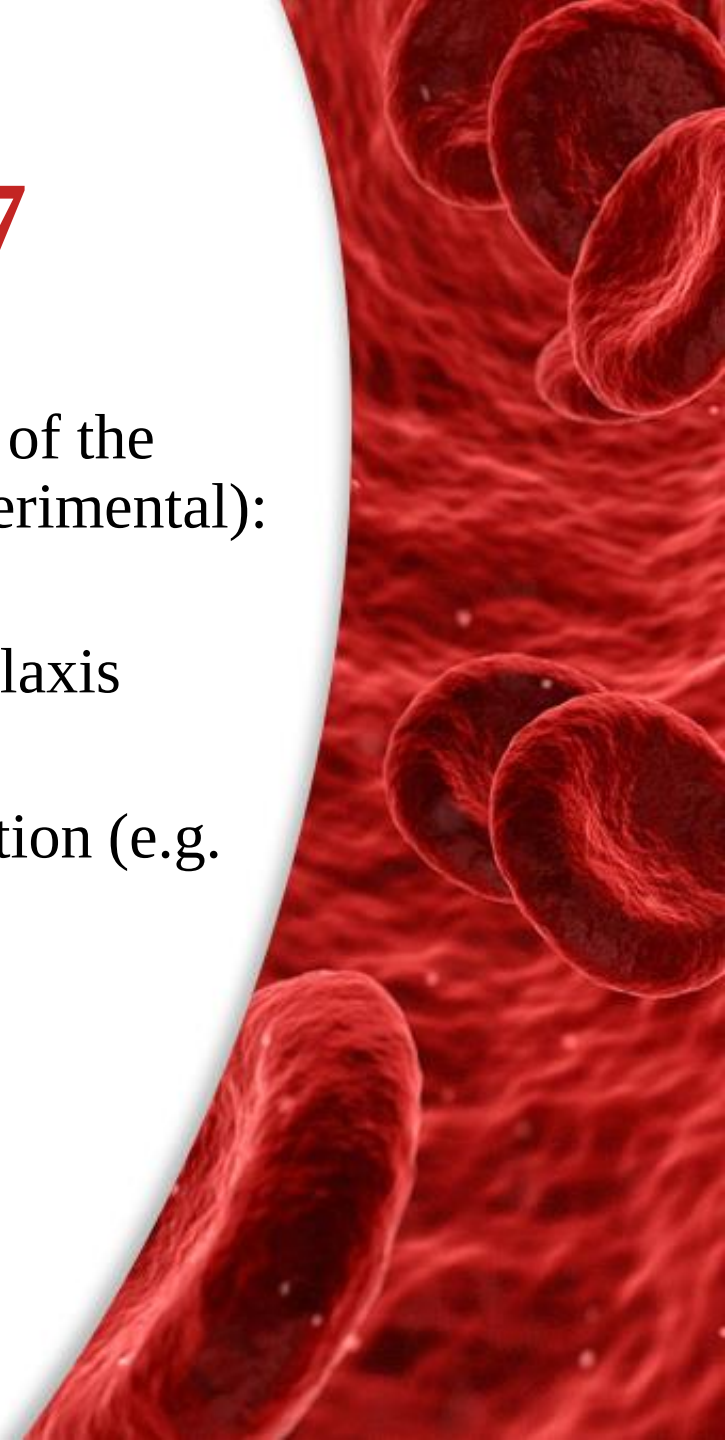
Therapeutic options in CGD

- Prophylaxis and treatment for infections.
- Hematopoietic stem cell transplantation.

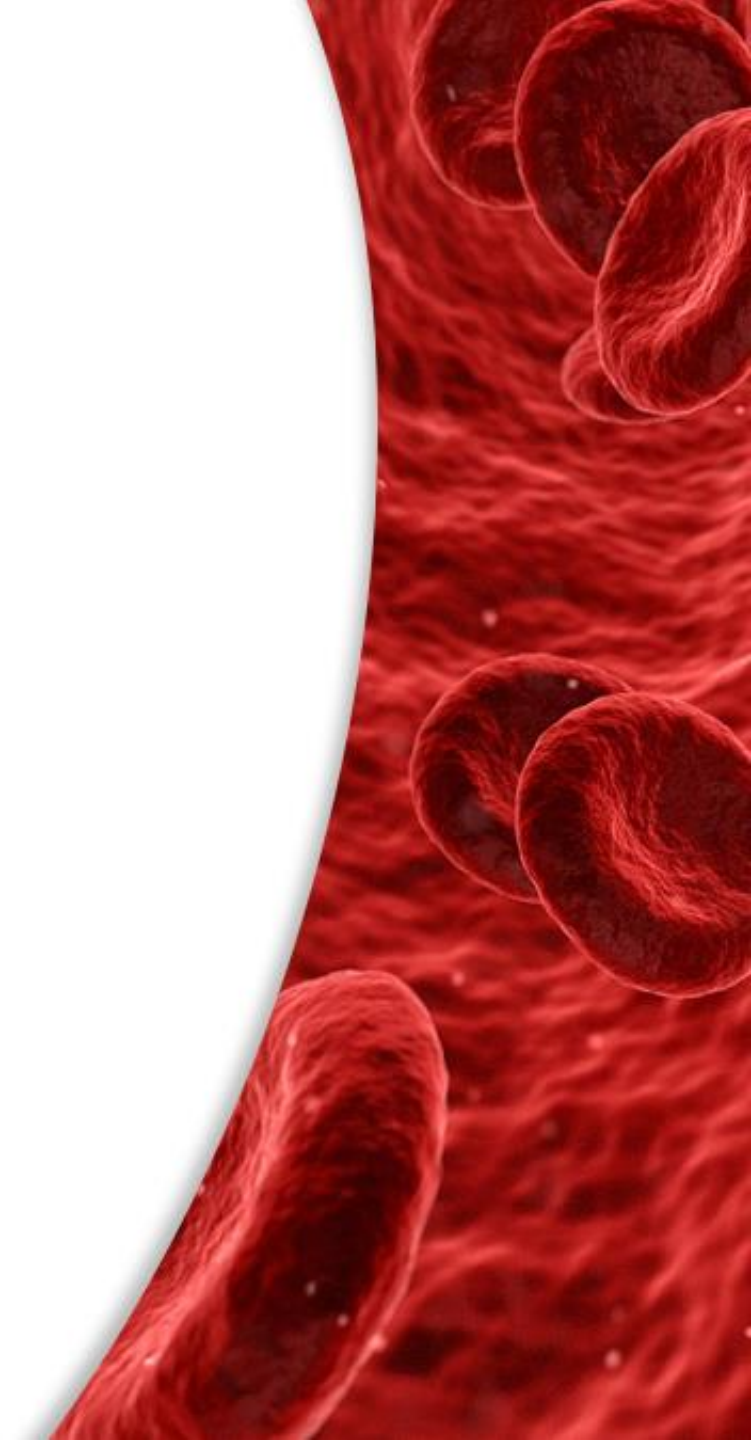


ESID EBMT HSCT guideline 2017

- X-CGD or A/R-CGD with MSD, MUD, MMUD donors plus one of the following (UCB and haploidentical stem cell sources are still experimental):
  - Non-availability of specialist medical care
  - Non-compliance with long-term antibiotic/antimycotic prophylaxis
  - ≥ 1 life-threatening infection in the past
  - Severe granulomatous disease with progressive organ dysfunction (e.g. lung restriction)
  - Steroid-dependent granulomatous disease (e.g. colitis)

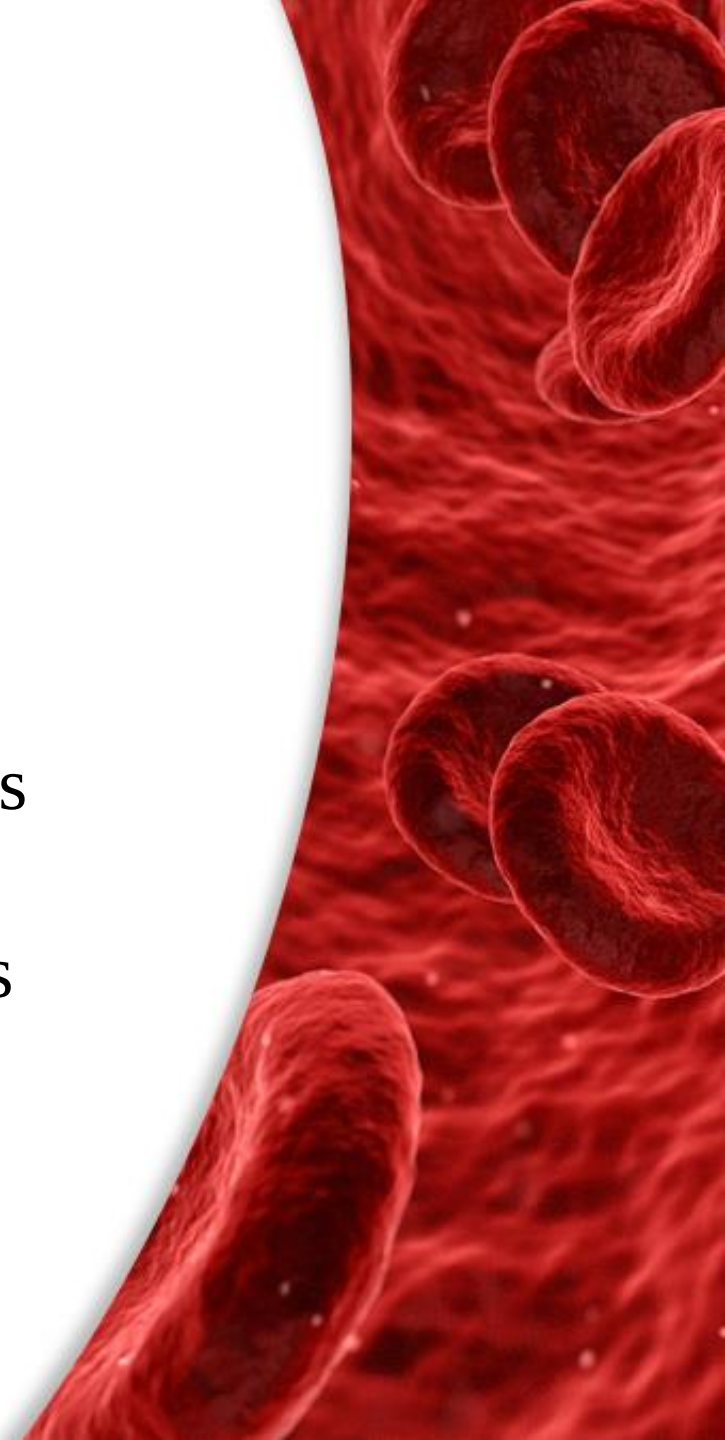


Conventional treatment
vs
Stem cell transplantation



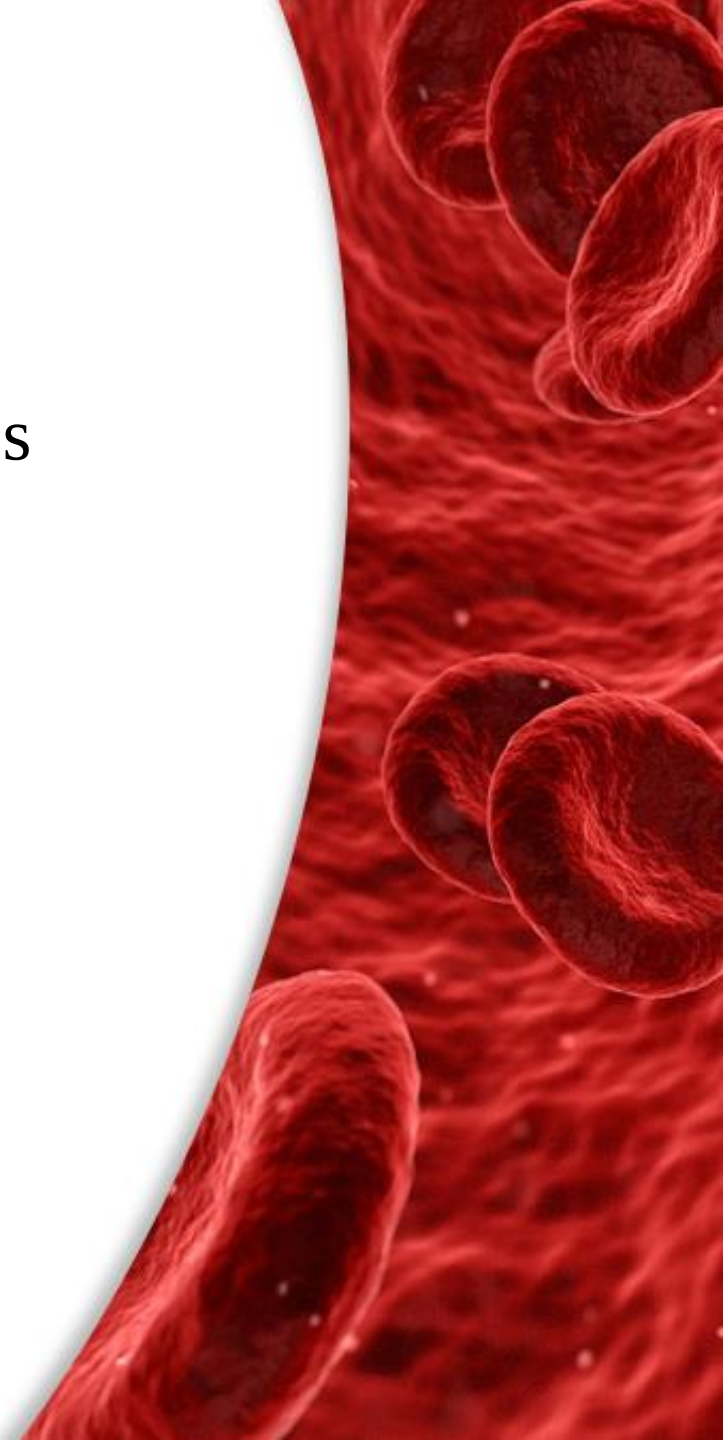
Conventional therapy or HSCT

- Conventional therapy aimed at preventing infection includes antibacterial prophylaxis, antifungal prophylaxis, and interferon γ therapy.
- Although allogeneic HCT is an established curative treatment for CGD, HCT is not performed for all patients with CGD.
- It is challenging to predict the future outcome of patients diagnosed with CGD given continuously improving treatment modalities.



Conventional therapy or HSCT

- Similar to conventional therapy outcomes, mortality rates of patients with CGD who have undergone HCT have decreased also:
  - High-resolution molecular HLA typing
  - RIC/RTC regimens.



Conventional therapy or HSCT

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ORIGINAL ARTICLE

Role of Allogeneic Hematopoietic Stem Cell Transplant for Chronic Granulomatous Disease (CGD): a Report of the United States Immunodeficiency Network

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Conventional therapy or HSCT

Abstract

Purpose Chronic granulomatous disease (CGD) is a primary immunodeficiency for which allogeneic hematopoietic stem cell transplant (HSCT) offers potential cure. Direct comparison of HSCT to non-HSCT management in the North American population was performed to identify clinical factors associated with overall survival (OS) and transplant-related survival (TRS).

Methods Retrospective review of CGD subjects enrolled in the United States Immunodeficiency Network. Survival was estimated by the Kaplan-Meier method and modeled by proportional hazards regression.

Results We identified 507 patients (66% *CYBB* mutants) diagnosed in 1953–2016. Fifty underwent allogeneic HSCT. Median follow-up was 9.1 years after diagnosis (0–45.8 years). OS was negatively associated with *CYBB* mutation (HR = 6.25; $p = 0.034$) and not associated with HSCT (88% v. 85% ± HCT) (HR = 1.26; $p = 0.65$). Transplant at ≤14 years old was associated with improved TRS (93% v. 82% at $T + 60$ months) (HR = − 4.51; $p = 0.035$). Patients transplanted before 15 years old had fewer severe infections pre-HSCT (mean 0.95 v. 2.13; $p = 0.047$). No mortality was reported in patients receiving stem cells from matched siblings. Infection incidence declined post-HSCT in subjects with greater than or equal to four infections pre-HSCT ($p = 0.0010$). Compared to non-HSCT patients ≥15 years old, post-transplant survivors had higher mean performance score (93.2 v. 85.9; $p = 0.0039$) and lower frequency of disability (11% v. 52%; $p = 0.014$).

Conclusion Allogeneic HSCT was associated with reduced infection incidence and improved functional performance, but not with a change in overall survival. Transplant-related survival was elevated in patients undergoing HSCT before 15 years old. Consider HSCT prior to late adolescence in patients with severely diminished reactive oxygen intermediate synthesis, particularly if a matched sibling is available.

Conventional therapy or HSCT

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ORIGINAL ARTICLE

WILEY

Outcome of chronic granulomatous disease - Conventional treatment vs stem cell transplantation

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Conventional therapy or HSCT

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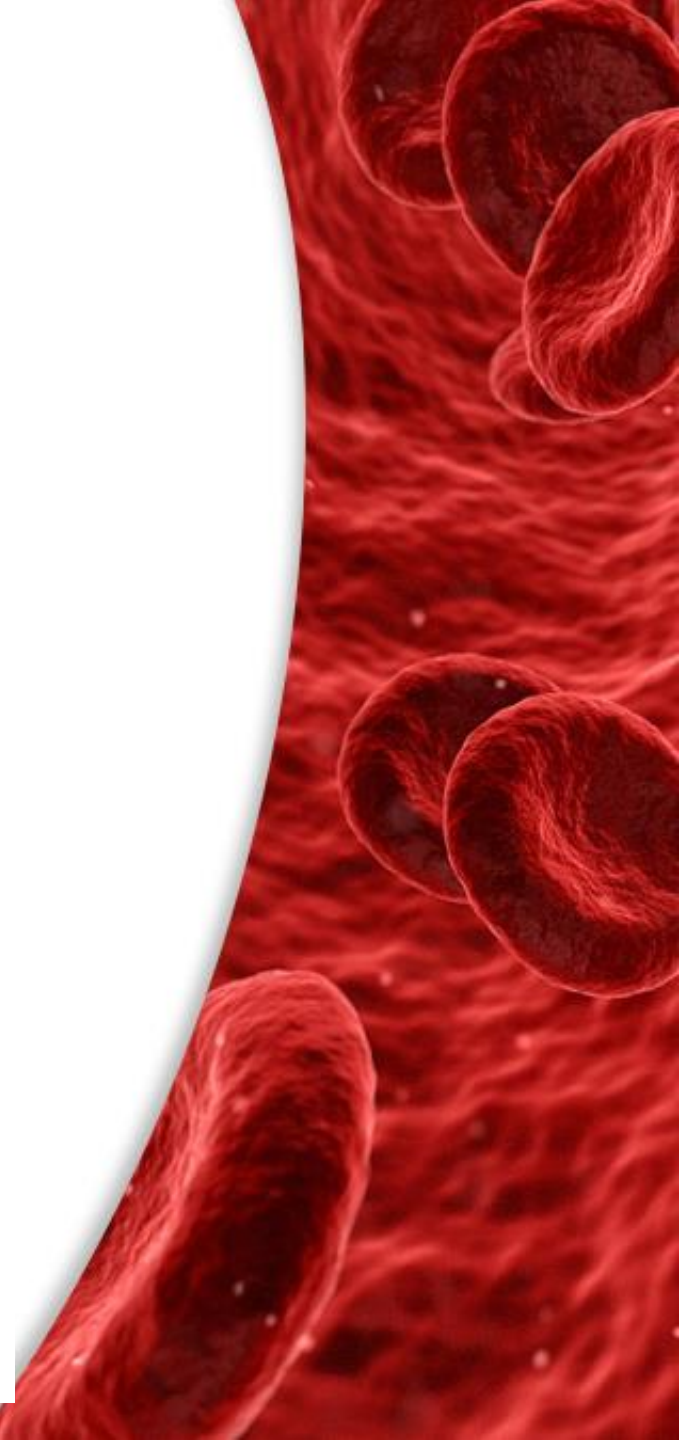
Abstract

Background: Hematopoietic stem cell transplantation (HSCT) can cure chronic granulomatous disease (CGD), but it remains debated whether all conventionally treated CGD patients benefit from HSCT.

Methods: We retrospectively analyzed 104 conventionally treated CGD patients, of whom 50 patients underwent HSCT.

Results: On conventional treatment, seven patients (13%) died after a median time of 16.2 years (interquartile range [IQR] 7.0-18.0). Survival without severe complications was 10 ± 3% (mean ± SD) at the age of 20 years; 85% of patients developed at least one infection, 76% one non-infectious inflammation. After HSCT, 44 patients (88%) were alive at a median follow-up of 2.3 years (IQR 0.8-4.9): Six patients (12%) died from infections. Survival after HSCT was significantly better for patients transplanted ≤8 years (96 ± 4%) or for patients without active complications at HSCT (100%). Eight patients suffered from graft failure (16%); six (12%) developed acute graft-vs-host disease requiring systemic treatment. Conventionally treated patients developed events that required medical attention at a median frequency of 1.7 (IQR 0.8-3.2) events per year vs 0 (IQR 0.0-0.5) in patients beyond the first year post-HSCT. While most conventionally treated CGD patients failed to thrive, catch-up growth after HSCT in surviving patients reached the individual percentiles at the age of diagnosis of CGD.

Conclusion: Chronic granulomatous disease patients undergoing HSCT until 8 years of age show excellent survival, but young children need more intense conditioning to avoid graft rejection. Risks and benefits of HSCT for adolescents and adults must still be weighed carefully.



Conventional therapy or HSCT

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Regular Article

TRANSPLANTATION

Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults

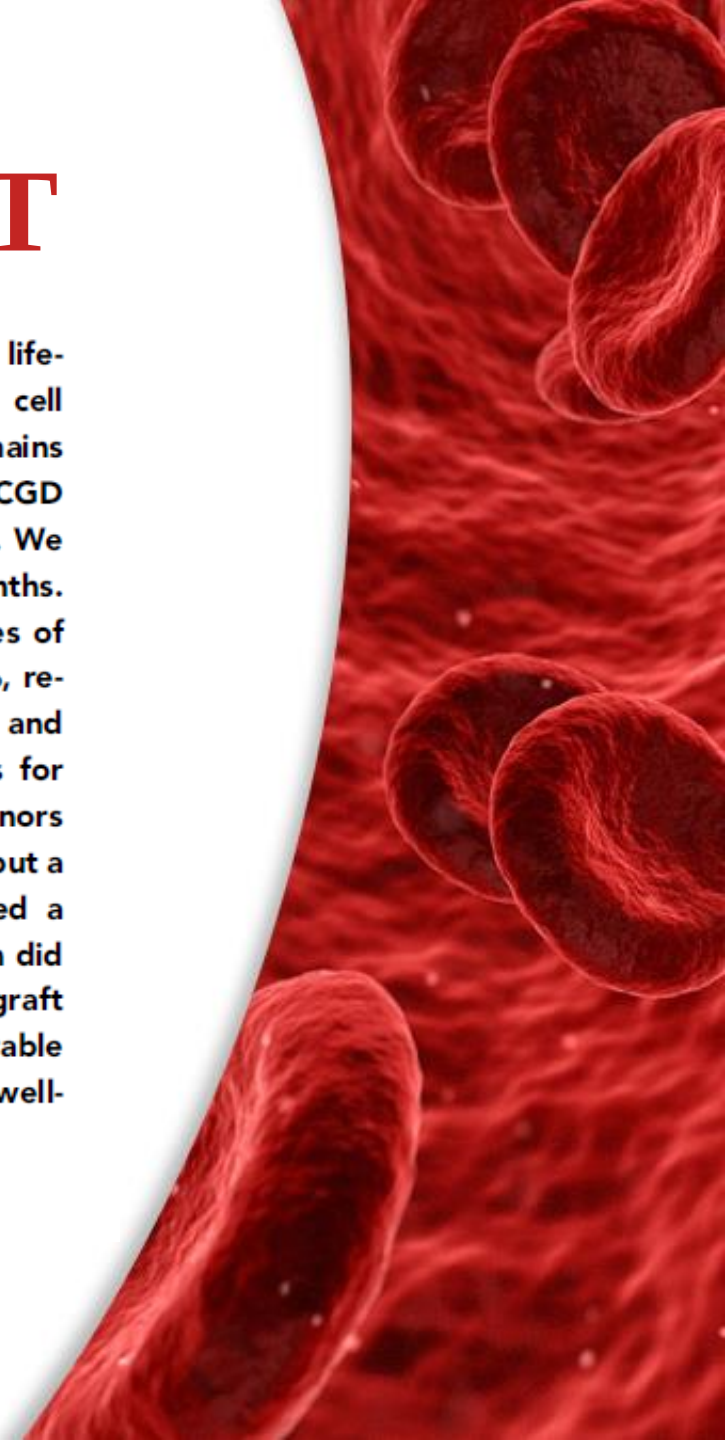
Robert Chiesa,[1] Junfeng Wang,[2,3] Henric-Jan Blok,[2] Sheree Hazelaar,[2] Benedicte Neven,[4] Despina Moshous,[4] Ansgar Schulz,[5] Manfred Hoenig,[5] Fabian Hauck,[6] Amal Al Seraihy,[7] Jolanta Gozdzik,[8] Per Ljungman,[9] Caroline A. Lindemans,[10,11] Juliana F. Fernandes,[12,13] Krzysztof Kalwak,[14] Brigitte Strahm,[15] Urs Schanz,[16] Petr Sedlacek,[17] Karl-Walter Sykora,[18] Serap Aksoylar,[19] Franco Locatelli,[20] Polina Stepensky,[21] Robert Wynn,[22] Su Han Lum,[23,24] Marco Zecca,[25] Fulvio Porta,[26] Mervi Taskinen,[27] Brenda Gibson,[28] Susanne Matthes,[29] Musa Karakukcu,[30] Mathias Hauri-Hohl,[31] Paul Veys,[1] Andrew R. Gennery,[23,32] Giovanna Lucchini,[1] Matthias Felber,[31] Michael H. Albert,[6] Dmitry Balashov,[33] Arjan Lankester,[24] Tayfun Güngör,[31,*] and Mary A. Slatter,[23,32,*] for the EBMT Inborn Errors Working Party

Conventional therapy or HSCT

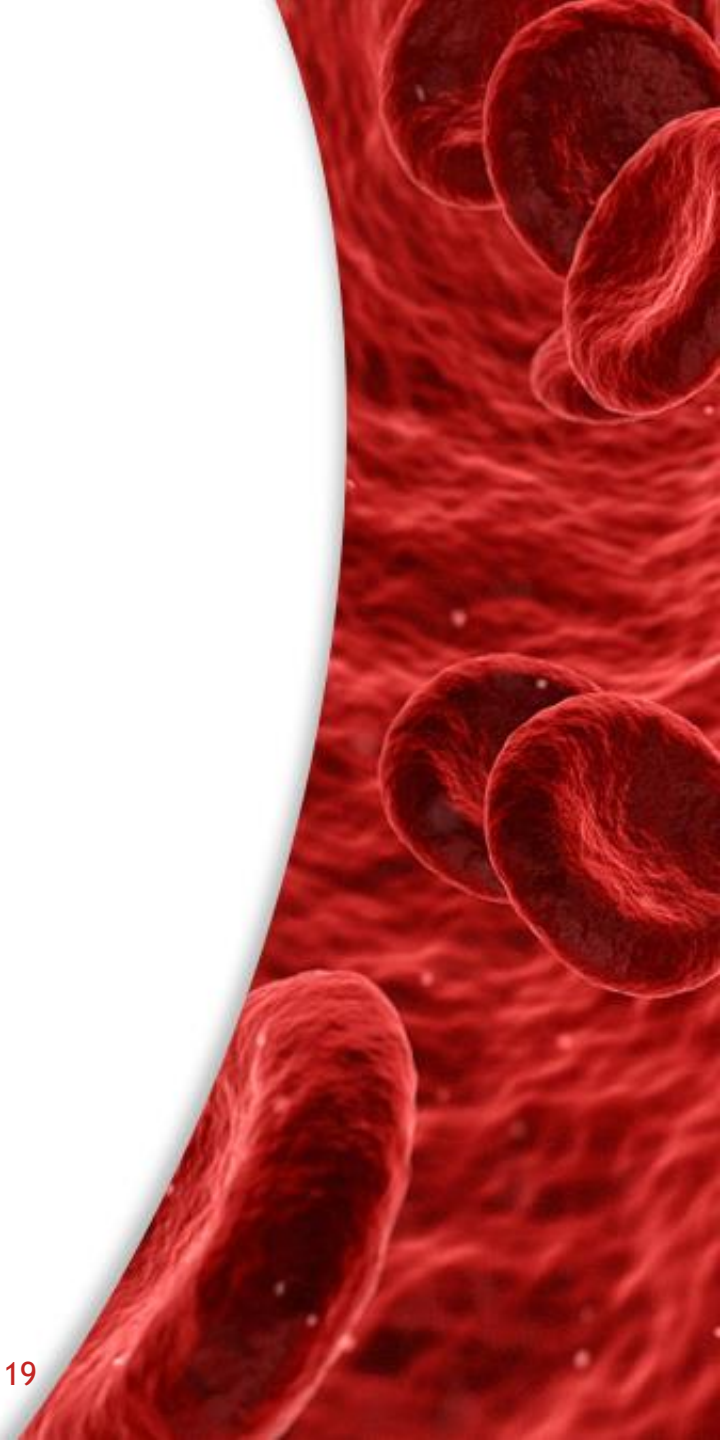
KEY POINTS

- An excellent outcome was obtained after allo-HCT in 712 patients with CGD, with a low incidence of graft failure and mortality.
- HCT for CGD should be strongly considered in young patients, particularly in the presence of a well-matched donor.

Chronic granulomatous disease (CGD) is a primary immunodeficiency resulting in life-threatening infections and inflammatory complications. Allogeneic hematopoietic cell transplantation (allo-HCT) can cure the disease, but the indication to transplant remains controversial. We performed a retrospective multicenter study of 712 patients with CGD who underwent allo-HCT transplantation from March 1993 through December 2018. We studied 635 children (aged <18 years) and 77 adults. Median follow-up was 45 months. Median age at transplantation was 7 years (range, 0.1-48.6). Kaplan-Meier estimates of overall survival (OS) and event-free survival (EFS) at 3 years were 85.7% and 75.8%, respectively. In multivariate analysis, older age was associated with reduced survival and increased chronic graft-versus-host disease. Nevertheless, OS and EFS at 3 years for patients ≥18 years were 76% and 69%, respectively. Use of 1-antigen-mismatched donors was associated with reduced OS and EFS . No significant difference was found in OS, but a significantly reduced EFS was noted in the small group of patients who received a transplant from a donor with a >1 antigen mismatch. Choice of conditioning regimen did not influence OS or EFS. In summary, we report an excellent outcome after allo-HCT in CGD, with low incidence of graft failure and mortality in all ages. Older patients and recipients of 1-antigen-mismatched grafts had a less favorable outcome. Transplantation should be strongly considered at a younger age and particularly in the presence of a well-matched donor. (*Blood.* 2020;136(10):1201-1211)



Characteristics and risks of HCT conditioning regimens



HCT conditioning regimens

Low Intensity

High Intensity

Reduced intensity conditioning

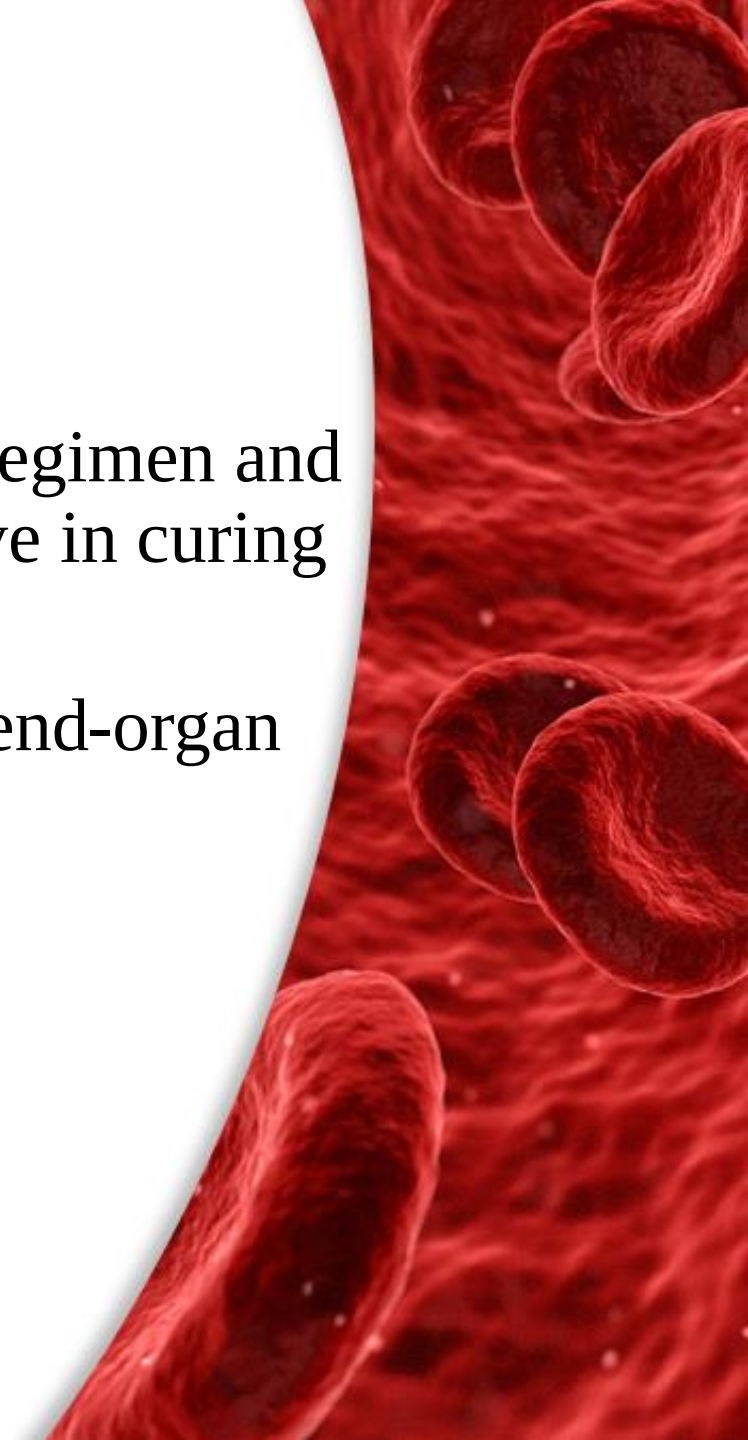
Myeloablative conditioning

- Decrease toxicities
- Reduction mortality
- Increased risk of non-engraftment

- Increase toxicities
- Increased level of disease control
- Quicker engraftment

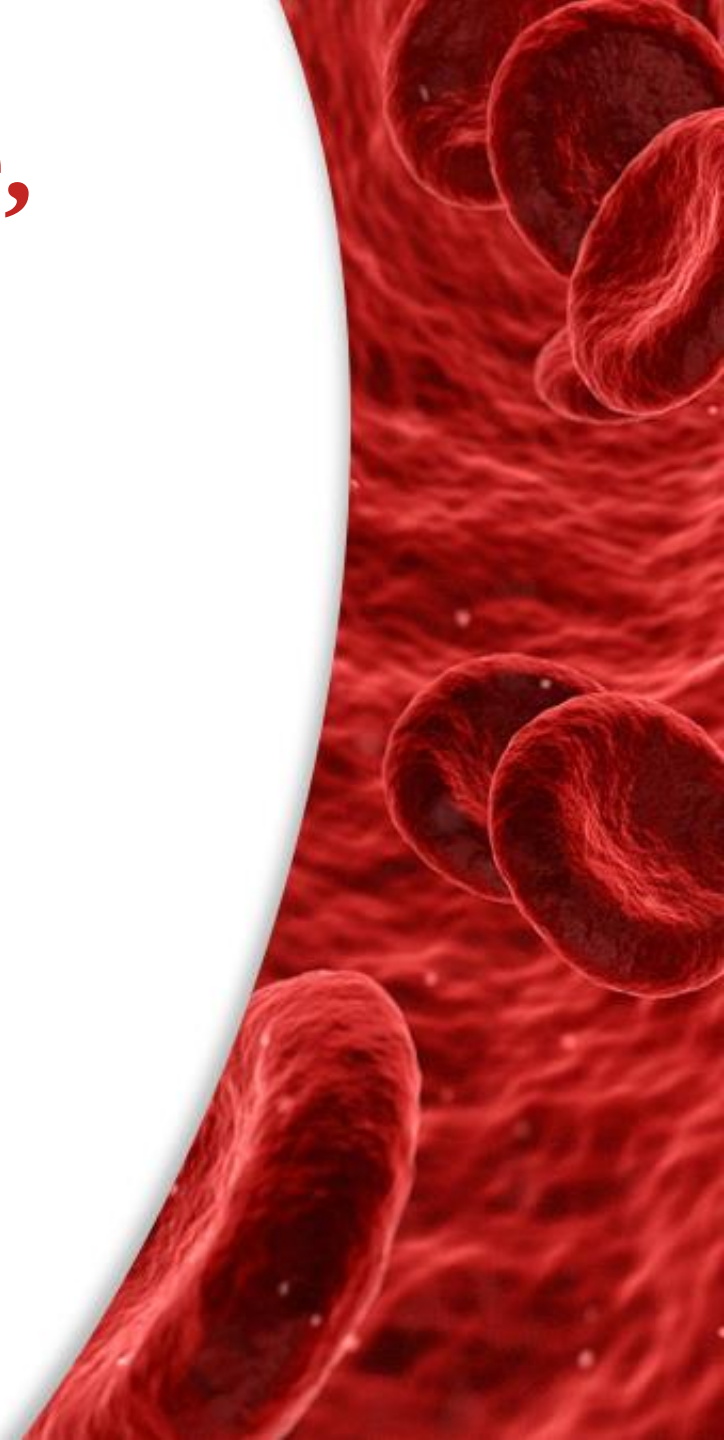
Experience with MAC HCT

- An MAC transplantation scheme with a busulfan-based regimen and using HLA-matched bone marrow donors is very effective in curing patients.
- Significant infections, inflammatory complications, and end-organ damage,
- Severe acute GVHD and death.

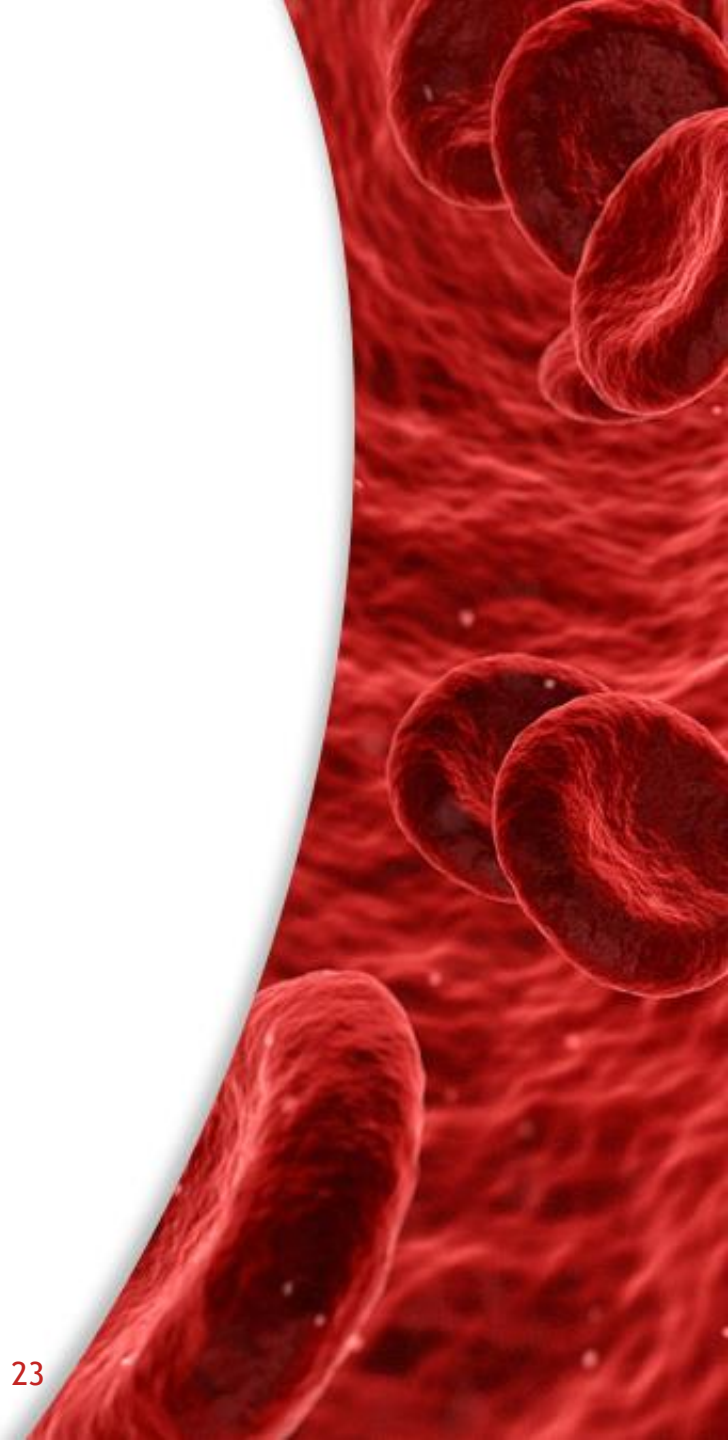


Experience with nonmyeloablative, RIC and RTC HCT

- RIC/RTC regimens are desirable
- Their potential to decrease treatment-related toxicity, especially for patients with an active infection and poor performance status at the time of transplant.
- Lower rates of acute GVHD
- High rates of mixed donor and recipient chimerism
- Increased rates of graft loss.

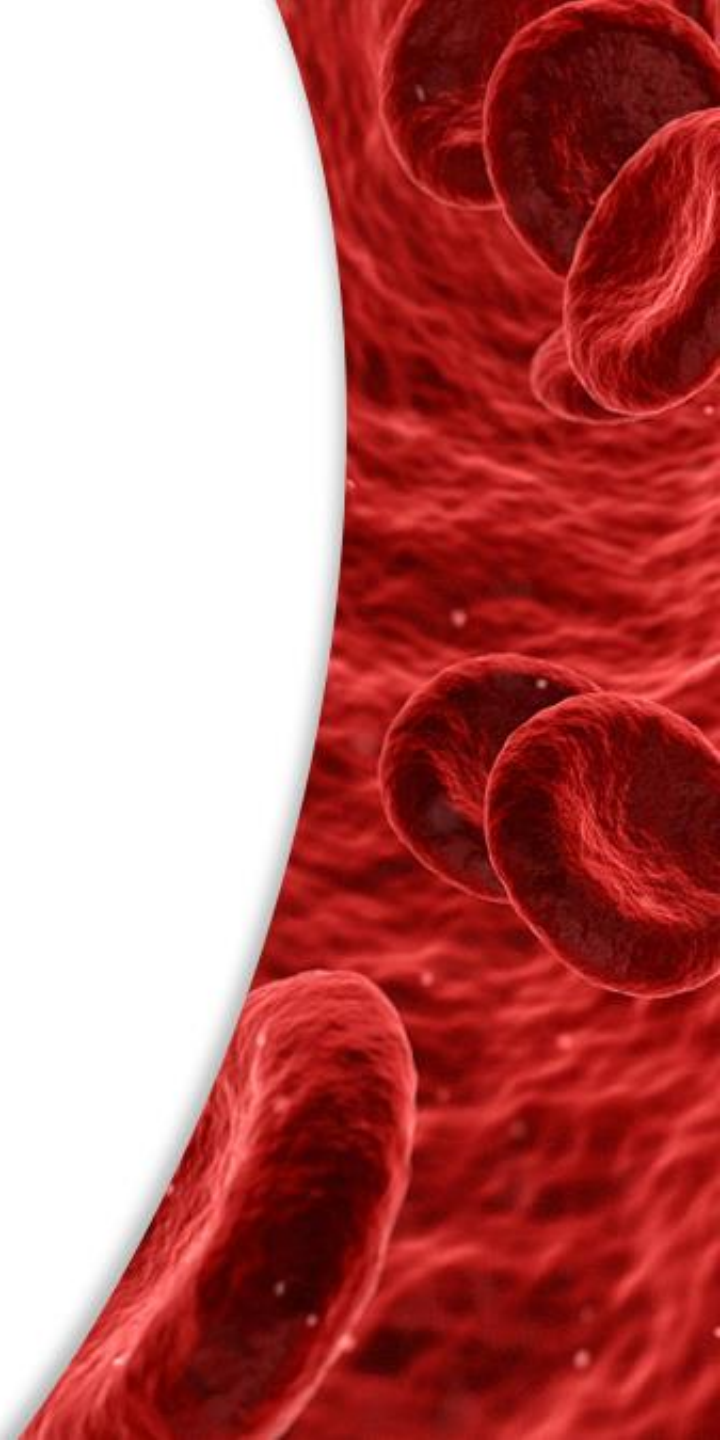


Chimerism

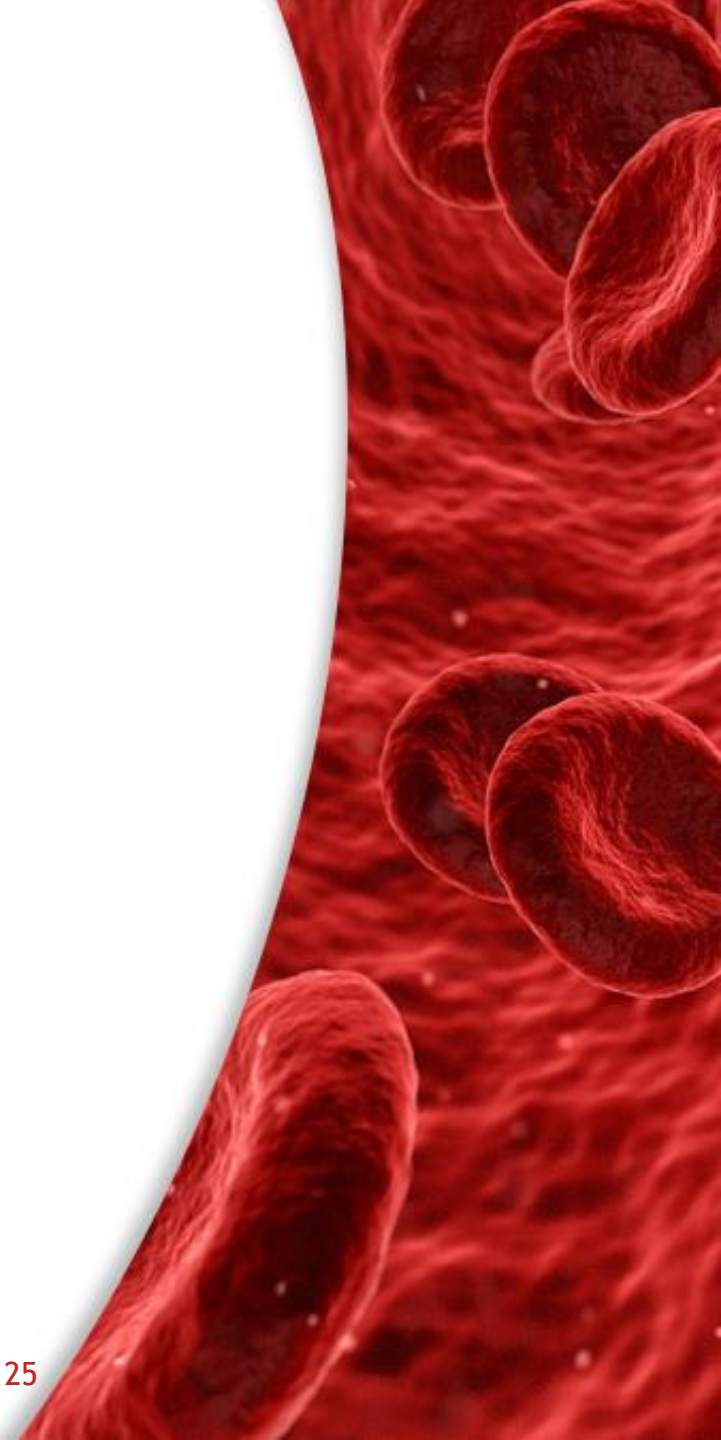


Mixed chimera

- This situation is acceptable for many patients with a primary immunodeficiency, because 100% correction of any immune defect usually is not needed.

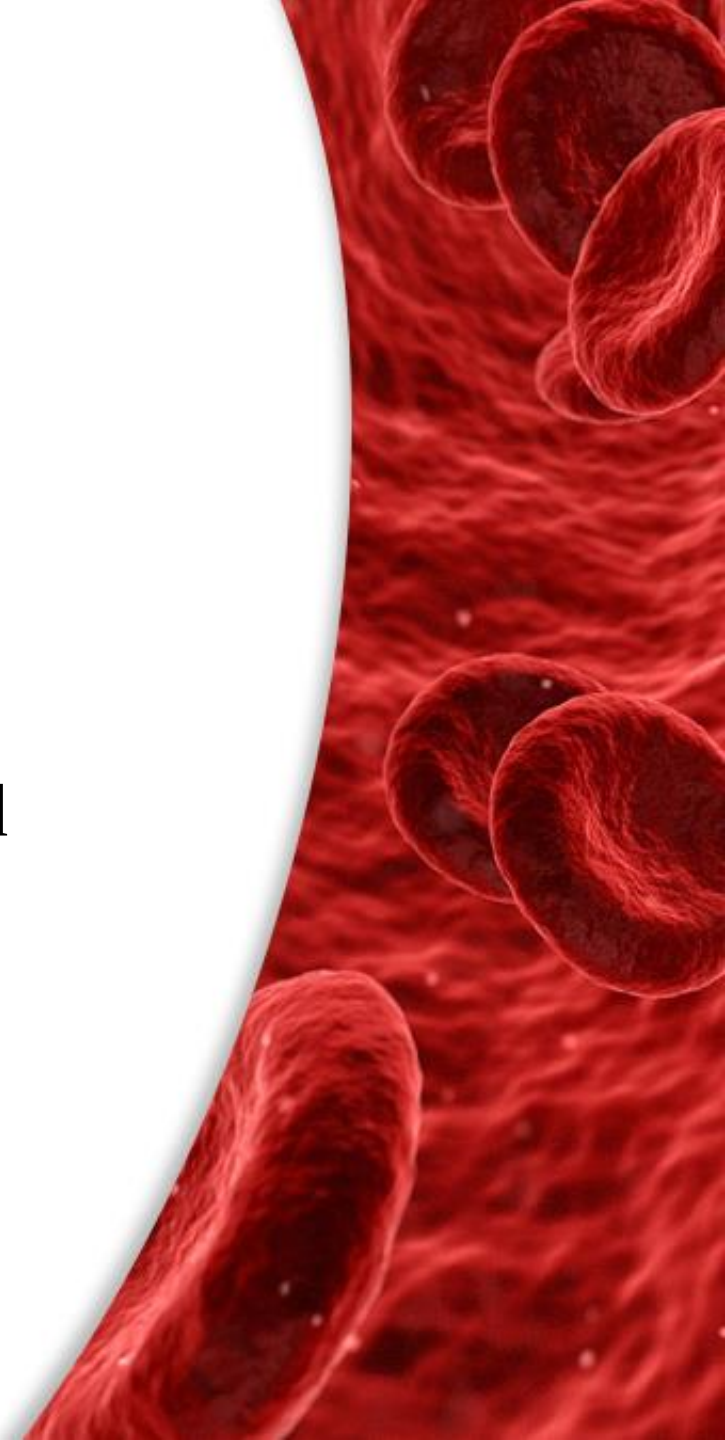


Challenges



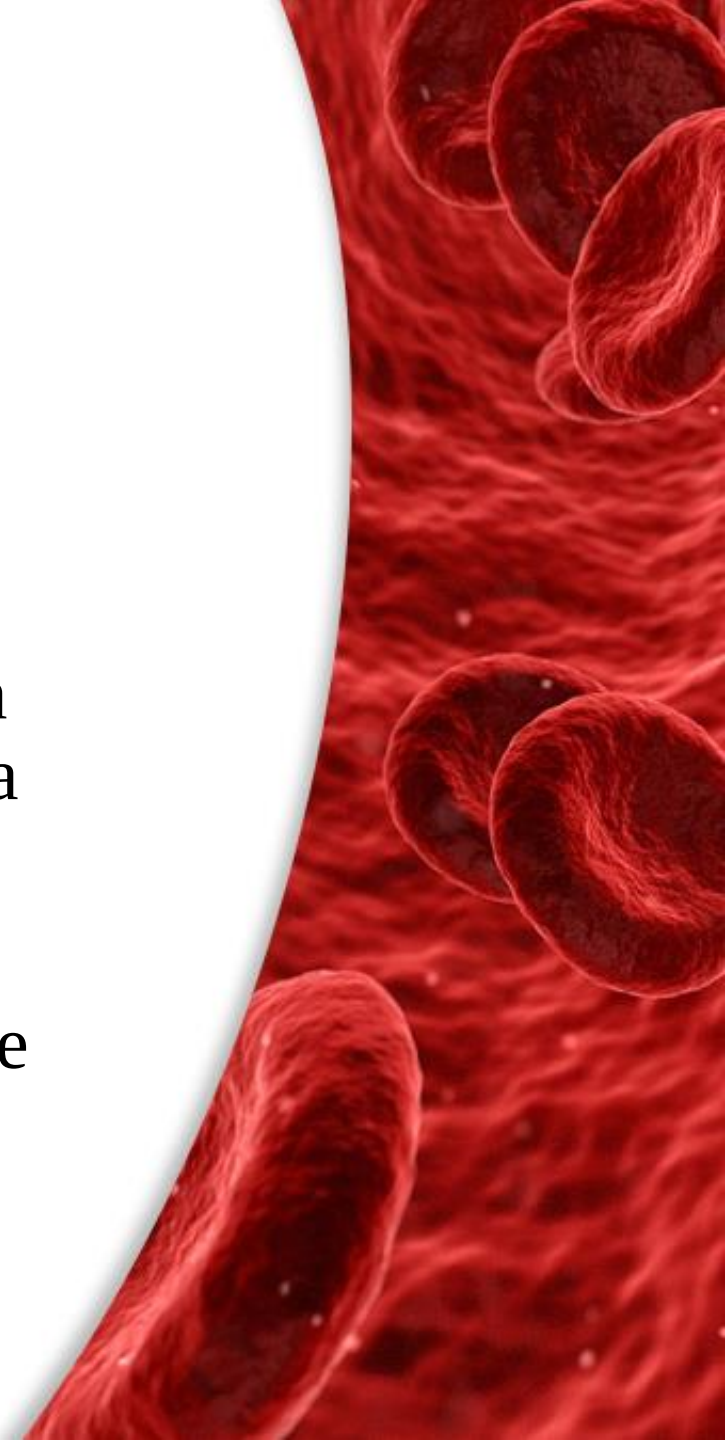
Challenges

- Reduction of infection and active autoimmunity or inflammation before transplantation is ideal.
- Complete resolution is impossible.
- RIC regimens enable transplantation during ongoing infection and result in potentially fewer infection-related deaths.



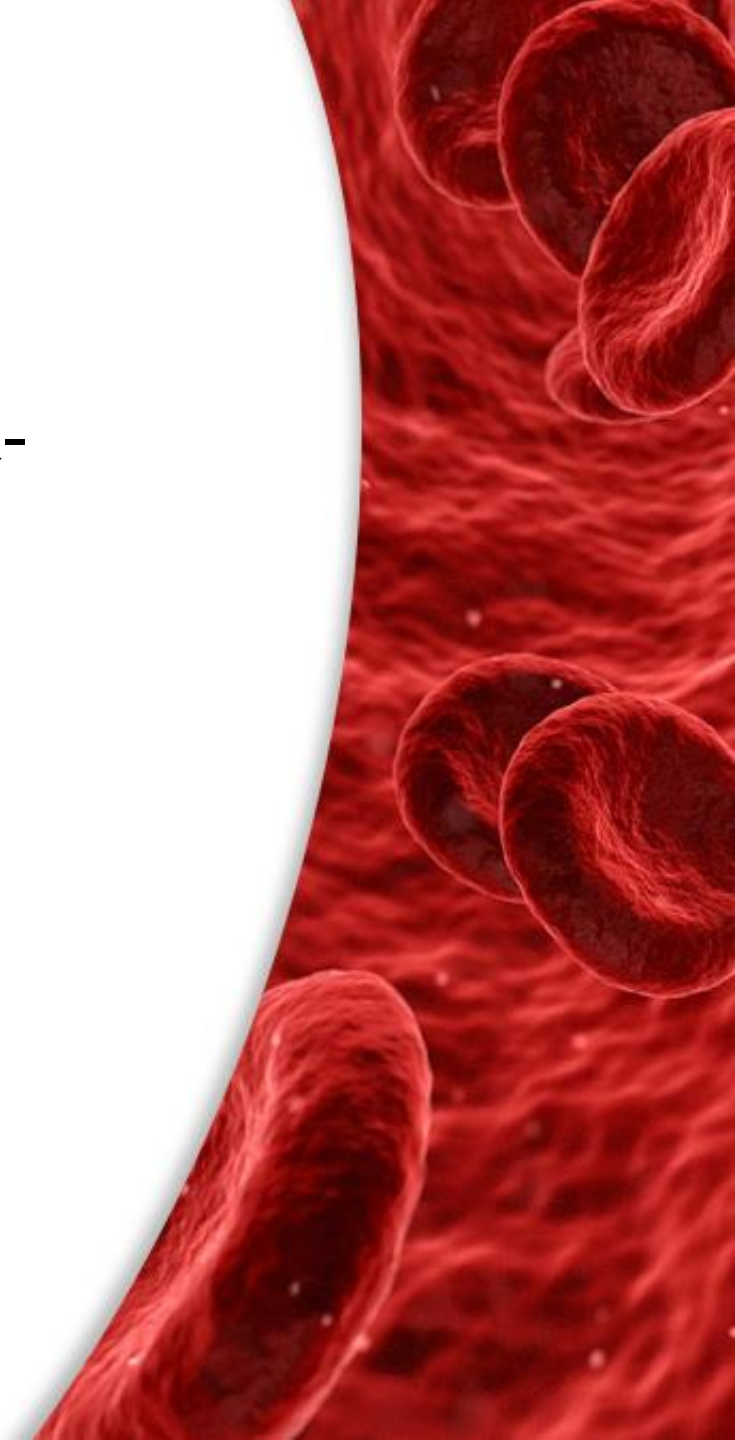
Challenges

- X-linked CGD: the possibility for McLeod phenotype:
  - secondary to deletion of the XK gene that results in absent production of the XK protein.
- The XK protein is essential for Kell antigen presentation on red cells, and patients with McLeod phenotype have a Kell-negative red cell phenotype.
- Patients with McLeod phenotype can have red cell antigen sensitization from previous Kell and XK-positive red cell transfusions and require special attention when an HCT is planned for them.



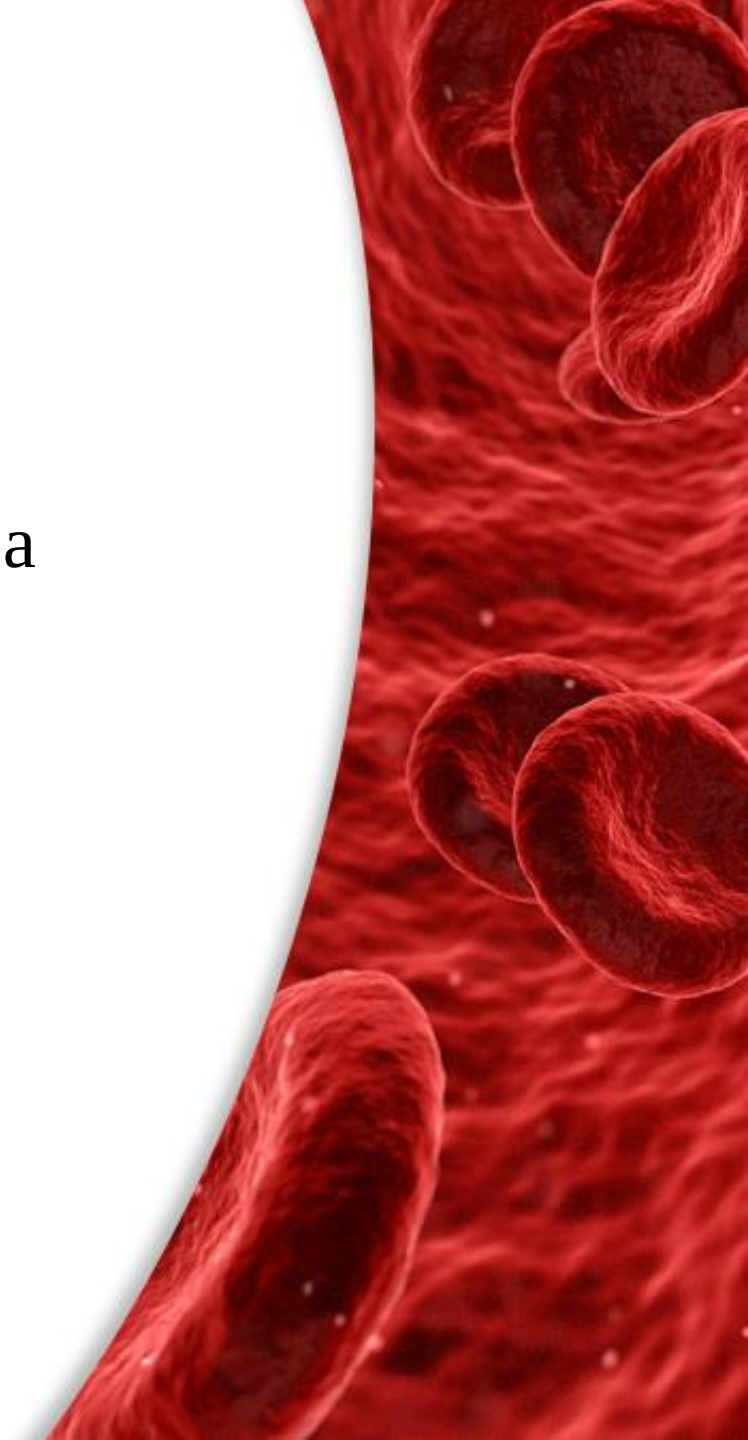
Challenges - McLeod phenotype

- Pretreatment with rituximab to reduce anti-Kell and anti-Kx.
- Conditioning with an MAC regimen with immune ablation to prevent persistent posttransplant recipient anti-Kell and anti-Kx B and T cells.
- Red cell reduction for Kell/Kx-positive stem cell products.
- Planned availability of Kell/Kx-negative (McLeod phenotype) blood to support the patient.



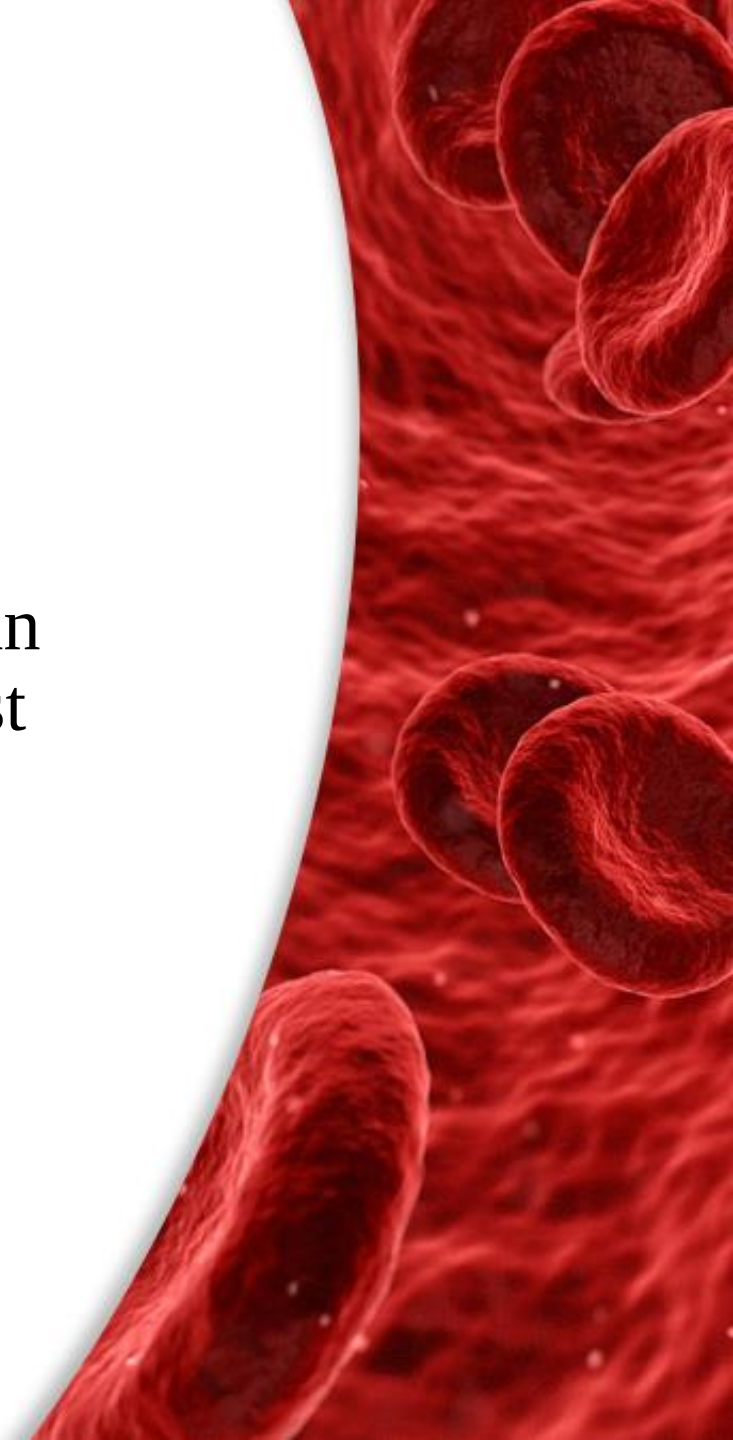
Challenges

- CGD is a nonmalignant disorder.
- We prefer to schedule the transplant to be performed in a summer month when possible.



Future

- The prevalence of CGD in Iran is increasing
  - consanguineous marriages.
- Overall, hereditary AR-CGD is more predominant in Iran rather than the XL-CGD form which is prevalent in most other countries.
  - reflects the high incidence of consanguineous marriages in Iran.



Nilsa & Arman


((The future is certainly looking brighter for patients with CGD))
((We hope that survival for every patient can be realized one day))